(19) World Intellectual Property Organization

International Bureau





(43) International Publication Date 13 October 2005 (13.10.2005)

PCT

(10) International Publication Number WO 2005/095410 A1

- (51) International Patent Classification⁷: C07D 493/04, 307/20, C07H 15/04
- (21) International Application Number:

PCT/EP2005/051452

- **(22) International Filing Date:** 31 March 2005 (31.03.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:

04101336.8 31 March 2004 (31.03.2004) E

- (71) Applicant (for all designated States except US): TI-BOTEC PHARMACEUTICALS Ltd. [—/IE]; Little Island, Co Cork (IE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): QUAEDFLIEG, Peter, Jan, Leonard, Mario [NL/NL]; Brahmslaan 13, NL-5583 ZG Waalre (NL). KESTELEYN, Bart, Rudolf, Romanie [BE/BE]; Weidelandstraat 18, B-9290 Berlare (BE). VIJN, Robert, Jan [NL/NL]; Leeuwerikstraat 48, NL-5922 VM Venlo (NL). LIEBREGTS, Constantinus, Simon, Maria [NL/NL]; Holterbergweide 14, NL-5709 MP Helmond (NL). KOOISTRA, Jacob, Hermanus, Matheus, Hero [NL/NL]; Parkweg 16, NL-9751 CS Haren (NL). LOMMEN, Franciscus, Alphons, Marie [NL/NL]; van Bronckhorststraat 78, NL-5961 SM Horst (NL).
- (74) Agent: DAELEMANS, Frank; Tibotec-Virco Comm. VA, Generaal De Wittelaan L 11B 3, B-2800 Mechelen (BE).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,

GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

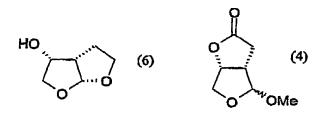
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR THE PREPARATION OF (3R,3aS,6aR) HEXAHYDRO-FURO[2,3-b]FURAN-3-OL



(57) Abstract: The present invention relates to methods for the preparation of diastereomerically pure (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol (6) as well as a novel intermediate, (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one (4) for use in said methods. More in particular the invention relates to a stereoselective method for the preparation of diastereomerically pure (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol, as well as methods for the crystallization of (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan- 2-one and for the epimerization of (3aR,4R,6aS) 4-methoxy-tetrahydro-furoly